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MiniReview

Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication – A Systematic Review with Meta-Analyses of Randomised Trials

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Abstract: Flumazenil is used for the reversal of benzodiazepine overdose. Serious adverse events (SAEs) including seizures and cardiac arrhythmias have been reported in patients treated with flumazenil, and the clinical advantage of flumazenil treatment has been questioned. The objective was to assess the risk of (S)AEs associated with the use of flumazenil in patients with impaired consciousness due to known or suspected benzodiazepine overdose. Studies included in the meta-analyses were identified by literature search in Medline, Cochrane Library and Embase using combinations of the words flumazenil, benzodiazepines, anti-anxiety agents, poisoning, toxicity and overdose. Randomised clinical trials (RCTs) in verified or suspected benzodiazepine overdose patients comparing treatment with flumazenil *versus* placebo were included. Pre-defined outcome measures were AEs, SAEs and mortality. Thirteen trials with a total of 994 randomised (990 evaluable) patients were included. AEs were significantly more common in the flumazenil group (138/498) compared with the placebo group (47/492) (risk ratio: 2.85; 95% confidence interval: 2.11–3.84; $p < 0.00001$). SAEs were also significantly more common in the flumazenil group compared with the placebo group (12/498 *versus* 2/492; risk ratio: 3.81; 95% CI: 1.28–11.39; $p = 0.02$). The most common AEs in the flumazenil group were agitation and gastrointestinal symptoms, whereas the most common SAEs were supraventricular arrhythmia and convulsions. No patients died during the blinded phase of the RCTs. The use of flumazenil in a population admitted at the emergency department with known or suspected benzodiazepine intoxication is associated with a significantly increased risk of (S)AEs compared with placebo. Flumazenil should not be used routinely, and the harms and benefits should be considered carefully in every patient.

Drug overdose is a frequently encountered challenge in emergency departments, and often benzodiazepines are involved either as single- or multi-drug intoxication.

Single-drug intoxication with benzodiazepines frequently causes unconsciousness; however, mortality is low. Symptoms might last several days due to the long half-life of some benzodiazepines (up to 70 hr for diazepam). When part of a multi-drug intoxication with other drugs or ethanol, prognosis is worse, and there are several reports of deaths due to multi-drug intoxications where benzodiazepines were involved [1–3].

Flumazenil, a 1,4-imidazobenzodiazepine, blocks the benzodiazepine receptors, with only a weak intrinsic action (GABA-A receptor complex) [4–8]. Flumazenil is used in the treatment of benzodiazepine overdose, primarily to reverse the sedative effect of benzodiazepines and prevent respiratory depression [4–6,9,10].

Initially, flumazenil was considered a safe antidote with no intrinsic activity and was not only recommended to reverse coma due to benzodiazepine overdose but also as a diagnostic tool in comatose patients in the emergency department [11,12]. Over the years, serious adverse events (SAEs) such as seizures and cardiac arrhythmias have been reported in patients treated with flumazenil [10,13], and there are several case reports of deaths associated with the use of flumazenil [14–16]. So far, it is unclear whether these incidents are related to the administration of flumazenil or the rapid resolution of benzodiazepine effects. The frequency of SAEs associated with the use of flumazenil is unknown. At the same time, benzodiazepine overdoses are only rarely considered life-threatening and might have seizure-protective effect when co-ingested with, for instance, tricyclic antidepressants, and treatment with a benzodiazepine antagonist can in these situations be potentially harmful. Therefore, it is of major importance to assess the potential risks associated with the use of flumazenil.

Objective

The objective of this study was to assess the risk of (S)AEs associated with the use of flumazenil in patients with impaired

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consciousness due to known or suspected benzodiazepine overdose.

Materials and Methods

Criteria for inclusion of studies.
We included randomised clinical trials conducted in patients admitted to an emergency department with impaired consciousness due to suspected or verified benzodiazepine overdose and treated with flumazenil or placebo. Studies were included whether the benzodiazepine overdose was intended or unintended and the overdose could be singularly of benzodiazepines or in combination with other drugs including alcohol. We excluded studies on animals, healthy volunteers, persons undergoing surgery, long-term users of benzodiazepines, patients who were not overdosed and patients who were chronically ill. Our pre-defined outcome measures were the number of AEs and SAEs including mortality.

Search methods.
We searched the literature using a pre-defined search strategy. The last search was performed in November 2014. We searched Medline, the Cochrane Library (CENTRAL) and Embase electronically using combinations of the words flumazenil, benzodiazepines, anti-anxiety agents, poisoning, toxicity and overdose. In addition, reference lists of relevant studies were screened.

Data collection and analyses.

1) Selection of studies: two authors (EP, GJ) independently selected eligible studies. Discrepancies between reviewers were discussed.
2) Data extraction and management: two authors (EP, GJ) independently recorded the following data from the included trials: (a) sample size (N); (b) gender and mean age of participants; (c) fraction of participants intoxicated with benzodiazepines; (d) dose of benzodiazepine intoxication; (e) co-intoxications; (f) flumazenil treatment regimes and average dose of flumazenil; (g) duration of the intervention; (h) open-label treatment with flumazenil; (i) type and number of (serious) adverse effects. In studies where the blinded phase was followed by an unblinded phase, only (S)AEs that occurred during the blinded phase were included in the meta-analyses.
3) Assessment of risk of bias in included studies: this was performed according to the Cochrane Collaboration tool for assessing risk of bias including allocation, blinding, incomplete outcome data and selective reporting [17].
4) Assessment of heterogeneity: heterogeneity was analysed using a chi-square test on N-1 degrees of freedom, with an α of 0.05 used for statistical significance and with the I^2 test. I^2 values of 25%, 50%, and 75% correspond to low, medium and high levels of heterogeneity.

We reported our findings in accordance with the PRISMA guidelines [18].

Results

Literature search.
The initial search resulted in a total of 915 references. Titles and abstracts were screened. Studies with irrelevant titles/abstracts were excluded. Of the 915 references, 44 were selected and, after manual search in the reference lists of these 44 articles, another 16 references were added. Manual search in the reference lists of these 16 articles gave additional 21 references. Of these 81 relevant articles, we retrieved full texts. Twenty-nine were original studies, and of these, 13 studies fulfilled our inclusion criteria and were included in the meta-analyses.

Description of studies.
The present meta-analyses included 13 trials with a total of 994 randomised (990 treated and evaluable) patients [11,19–30]. All trials were randomised, double-blind, placebo-controlled, prospective trials. Patients were randomised to active treatment with flumazenil (498 patients) or placebo (492 patients) (table 1). In all studies, inclusion criteria were adult patients admitted to the emergency departments or intensive care units with impaired consciousness due to a suspected or known benzodiazepine overdose, either as single-drug intoxication or as part of a multi-drug intoxication. All patients received basic acute and supportive treatment according to the patients' need and judgement of the treating physician. This included, but was not limited to emesis, gastric lavage and activated charcoal.

Three trials had exclusion criteria related to the use of benzodiazepines: known or suspected benzodiazepine overdose [21], known therapeutic use of benzodiazepines [20] and known hypersensitivity to benzodiazepines [27]. One trial excluded patients with the evidence of alcohol or tricyclic antidepressants (TCAs) ingestion [21], and four trials excluded patients with (severe) organic injury and/or liver or renal impairment [22,23,26,27]. Another four trials excluded patients with known or suspected brain trauma, new neurological findings or epilepsy [11,27–29]. Four trials did not inform about exclusion criteria [19,24,25,30].

Mean age in the trials included in the meta-analyses varied from 32 to 57 years. Five hundred and forty-two patients (54.7%) were females and 441 (44.5%) were males (gender was not informed for 7 (0.7%) patients).

In all included trials, a total of 720 patients (72.4%) were intoxicated with benzodiazepines. Ten studies provided information about single- *versus* multi-drug intoxication with benzodiazepine on total 596 patients, and of these, 205 patients suffered from a single-drug intoxication with benzodiazepines and 391 patients suffered from a multi-drug intoxication with the most common other drugs being: ethanol, anxiolytics (including barbiturates), opioids and TCAs [19,20,22–28,30]. Three studies did not provide information about co-ingested drugs [11,21,29]. Coma score was assessed at different scales with the most used being the (modified) Glasgow Coma Scale ((m)GCS).

Flumazenil treatment regimes differed between trials (table 1). All included trials administered flumazenil intravenously and initial dose of flumazenil varied from 0.1 mg to 2.5 mg. Total flumazenil dose varied from 1.0 to 10.0 mg (table 1). Nine studies informed about average used flumazenil dose, which varied from 0.77 to 7.13 mg (table 1) [20,22–24,26–30].

Observation time was reported in 9 studies. All these studies reported a short observation time ranging from 10 min. to maximally 24 hr (in two studies). Median and mean observation times in the nine studies were 5 and 8.5 hr, respectively.

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Table 1.

Characteristics of included studies.

Reference	Total number of patients	Number of patients treated with flumazenil	Number of patients treated with placebo	Flumazenil treatment regime initial dose (max. dose)	Average given dose of flumazenil
Aarseth *et al.* [19]	18	9	9	2.5 mg ×2 (max dose 5.0 mg)	No information
Barnett *et al.* [21]	45[1]	19	22	0.3 mg (max dose 2.0 mg)	No information
Flumazenil BIM Study Group [20]	326	162	164	0.2 + 0.3 mg +0.5 mg ×4 (max dose 3.0 mg)	2.4 mg ± 0.9 S.D.
Höjer *et al.* [22]	52	26	26	0.3 + 0.3 + 0.2 + 0.2 mg (max dose 1.0 mg)	0.77 mg
Höjer *et al.* [11]	105	53	52	1.0 mg (max dose 1.0 mg)	No information
Knudsen *et al.* [23]	32	16	16	0.3 + 0.3 + 0.2 + 0.2 mg (max dose 1.0 mg)	0.96 mg
Lheureux *et al.* [24]	20	10	10	0.1 mg ×10 (max dose 1.0 mg)	1,58 mg
Martens *et al.* [25]	26	14	12	1.0 or 5.0 mg ×1 (max dose 1.0 or 5.0 mg)	No information
O'Sullivan *et al.* [26]	60	31	29	0.3 + 0.3 + 0.2 + 0.2 mg (max dose 1.0 mg)	0.87 mg ± 0.18 S.D.
Rouzioux *et al.* [27]	86	41	45	0.5 + 0.5 mg +0.2 mg ×10 (max dose 3.0 mg)	1.52 mg ± 0.69 S.D.
Spivey *et al.* [28]	170	87	83	1.0 mg ×10 (max dose 10.0 mg)	7.13 ± 3.42 mg
Weinbroum *et al.* [29]	31	17	14	0.1 mg ×10 (max dose 1.0 mg)	0.8 mg ± 0.3 mg
Ritz *et al.* [30]	23	13	10	0.3 + 0.3 + 0.2 + 0.2 mg (max dose 1.0 mg)	0.87 mg[2]
Total	994[1]	498	492	Range max dose: 1.0–10.0 mg	Range: 0.8–7.14 mg

Flumazenil BIM Study Group = The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group, 1992.
[1]Four of these patients were excluded after randomization but before administration of study drug. There is no information regarding these four patients including information on which treatment they were allocated to.
[2]For six patients not included in the open label.

After the first double-blind phase, nine trials including 839 patients continued in a second phase with the possibility of open-label treatment with flumazenil to both the primary flumazenil-treated group and the placebo group [11,20,22,24,25,27–30]. Results from the second phase are not included in our meta-analyses.

Risk of bias in included studies.

Trial methodology was inadequately reported in the majority of trials, and no trials were considered to be trials with low risk of bias according to the Cochrane collaboration definitions [31] (table 2).

Effects of intervention.

Adverse events were significantly more common in the flumazenil-treated group compared with the non-intervention group: 138/498 in the flumazenil group *versus* 47/492 in the placebo-treated group (risk ratio (RR): 2.85; 95% confidence interval (CI): 2.11–3.84; $p < 0.00001$) (fig. 1). No heterogeneity was observed ($I^2 = 0\%$). The most commonly reported AEs in the flumazenil-treated group were agitation, anxiety and gastrointestinal symptoms (table 3).

Serious adverse events were also significantly more common in the flumazenil-treated group compared with the placebo group. Twelve of the 498 patients treated with flumazenil experienced SAEs compared to two of the 492 patients in the placebo-treated group (risk ratio: 3.81; 95% CI: 1.28–11.39; $p = 0.02$) (fig. 2). No heterogeneity was observed ($I^2 = 0\%$). In the flumazenil group, the reported SAEs were supraventricular arrhythmia (4 patients), unspecified tachycardia (3 patients), convulsions (3 patients), multiple ventricular beats (1 patient) and sudden fall in blood pressure with a systolic blood pressure of 60 mmHg (1 patient) (table 3). Two patients in the placebo-treated group experienced supraventricular arrhythmias. No patients in the flumazenil or in the non-intervention group died during the blinded phase of the randomised trials.

Discussion

These meta-analyses show that the use of flumazenil in patients referred to the ER with impaired consciousness due to known or suspected benzodiazepine overdose is associated with statistically significantly more AEs and SAEs compared with placebo. The most common SAEs were supraventricular arrhythmia and convulsions. No mortality was observed in either treatment arm during the blinded phase of the randomised trials.

Strengths.

The present study offers a number of advantages. Included studies were found by a systematic search in a number of databases and reference lists from relevant literature. Thereby, all relevant studies should have been included and selection bias was reduced. All studies and all data were extracted in duplicate.

The patient group included in these meta-analyses was considered representative for the majority of (benzodiazepine) intoxicated patients encountered in the emergency department, emphasizing the relevance of this study. In clinical practice, patients are often admitted without a known intoxication; therefore, the treating physicians do not always know whether the use of flumazenil is indicated or should be withhold. Likewise, it is often difficult to differentiate between symptoms due to the intoxication or adverse effects to flumazenil.

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Table 2.
Assessment of methodology quality/bias.

Reference	Allocation sequence	Allocation concealment	Blinding	Intention to treat	Incomplete outcome data addressed
Aarseth *et al.* [19]	Unclear	Unclear	Yes	No	Yes
Barnett *et al.* [21]	Yes	Yes	Yes	No	No
The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group [20]	Unclear	Unclear	Yes	No	Yes
Höjer *et al.* [22]	Unclear	Unclear	Yes	Yes	Yes
Knudsen *et al.* [23]	Unclear	Unclear	Yes	No	Yes
Lheureux *et al.* [24]	Unclear	Unclear	Yes	Yes	Yes
Martens *et al.* [25]	Unclear	Unclear	Yes	No	No
O'Sullivan *et al.* [26]	Yes	Unclear	Yes	Yes	Yes
Rouzioux *et al.* [27]	Unclear	Unclear	Yes	Yes	Yes
Spivey *et al.* [28]	Unclear	Unclear	Yes	No	Yes
Höjer *et al.* [11]	Unclear	Unclear	Yes	Yes	Yes
Weinbroum *et al.* [29]	Unclear	Unclear	Yes	Yes	Yes
Ritz *et al.* [30]	Unclear	Unclear	Yes	Yes	Yes

Table 3.
Reported adverse events and serious adverse events.

	Number of patients in flumazenil-treated group	Number of patients in placebo-treated group
Adverse events (AEs)		
Aggressive behaviour, agitation, screaming, restlessness	33	10
Local reaction at injection site	4	11
Nausea, vomiting, abdominal cramps	26	5
Sweating, shivering, unwell and the shakes, chills and hot flashes	9	2
Headache, dizziness	5	1
Anxiety, distress, depressed mood, abnormal crying, dysphoria	19	2
Tremor, quick muscular contractions	2	2
Unspecified AEs	28	12
TOTAL AEs	126	45
Serious adverse events (SAEs)		
Seizures/convulsions	3	0
Supraventricular arrhythmia	4	2
Multiple ventricular beats	1	0
Tachycardia	3	0
Sudden fall in systolic BP	1	0
TOTAL SAEs	12	2
TOTAL AEs + SAEs (= TOTAL (S)AEs)	138	47

Limitations.

The present study encompasses some methodological limitations. The quality and quantity of available evidence limits our findings and interpretations. All included trials had a high risk of bias, and furthermore, there might be risk of publication bias. The included studies were heterogeneous with different treatment regimes and different inclusion and exclusion criteria. In all studies, observation time was limited. Moreover, only a few patients with relatively few outcome measures were included in the trials; thus, there was a potential risk of random errors.

Our result is in accordance with a previously published meta-analysis of Ngo *et al.* [13] based on seven studies who also found a statistically significantly higher risk of both major AEs (RR: 2.86, 95% CI: 0.12–69.32) and minor AEs (RR: 3.47, 95% CI: 2.22–5.43).

The most common AEs related to flumazenil reported in the included studies were mild and transient AEs including nausea and vomiting and AEs that (partly) might mimic withdrawal symptoms (table 3). Although vomiting was registered as an AE in our review, one should remember that vomiting in intoxicated patients with comprised consciousness is associated with an increased risk of aspiration which can be considered as a SAE [32]. There were no reports of aspiration or aspiration pneumonia in the included trials, during neither the blinded nor the open phase of the trials. However, even when including the open phase of the trials, follow-up was short in all included studies. In the literature, there are three case reports of aspiration pneumonia related to flumazenil use, and in all cases, assisted ventilation and prolonged hospitalisation were necessary [33,34].

The most common SAEs were cardiac arrhythmias and convulsions. In the present meta-analyses, nine SAEs in the flumazenil group were related to the cardiovascular system. During the open phase of the trials, another eight cardiovascular SAEs were reported: two cases of hypotension [28], three cases of hypertension (blood pressure increased by 23–25%) [29], two cases of tachycardia (heart rate 120 bpm) [29] and one case of cardiac arrhythmia [20]. A literature search provided another four case reports of tachycardia and arrhythmia

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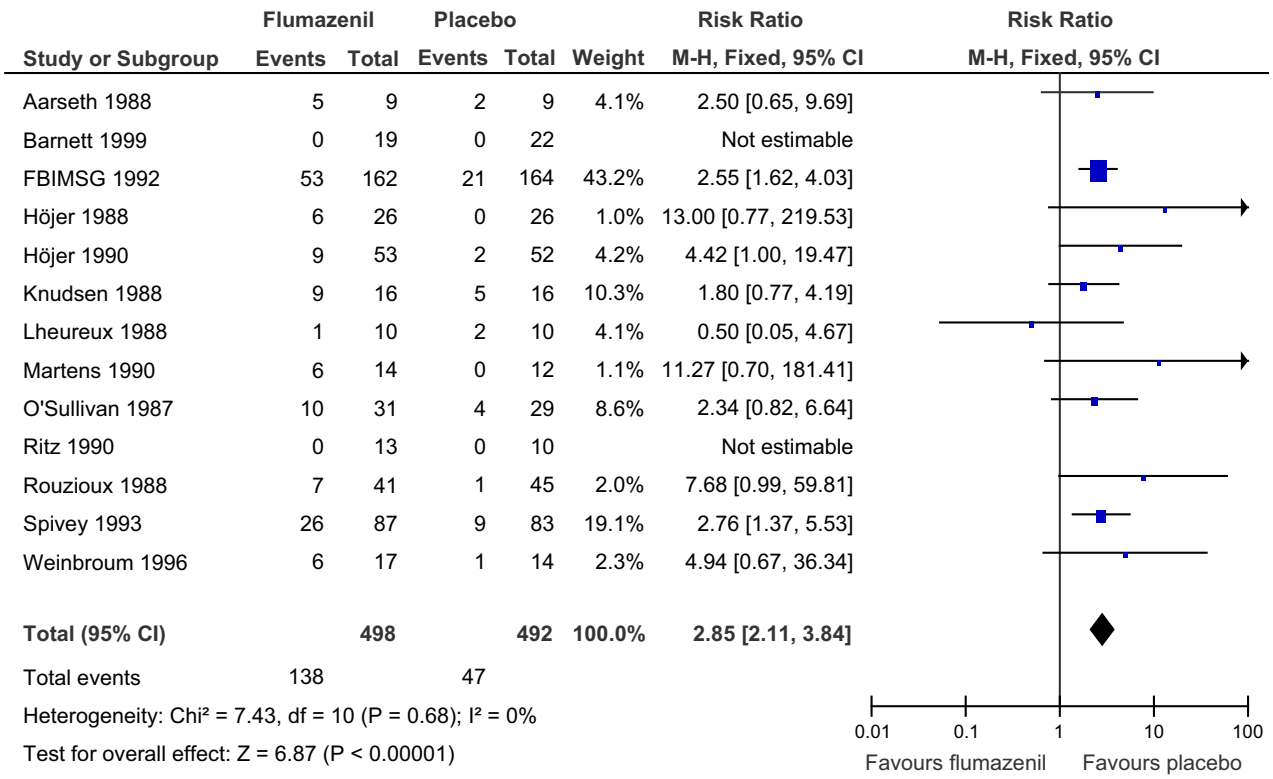

Fig. 1. Forrest plot, all adverse events.

related to the use of flumazenil, whereof one case of ventricular tachycardia within 20 min. progressed to asystole and death [15,35–37].

Holdcroft [38] investigated reported AEs related to anaesthetics and neuromuscular blocking drugs. They reported 14 cardiovascular AEs related to the use of flumazenil, and of these, two were cardiac arrest and one was ventricular fibrillation; all three patients died [38]. This emphasizes the potential morbidity and mortality related to cardiac AEs due to the use of flumazenil.

None of the randomised patients included in this meta-analyses died. During the open phase of the study, six patients died, all reported in the study by The Flumazenil Study Group [20]. All six deaths occurred 5 hr to 5 days after flumazenil had been administered [20]. One of the patients experienced seizures and cardiac arrest and died 5 hr after the administration of flumazenil. The patient was intoxicated with amoxapine and nortriptyline, and the investigator reported the convulsions to be possibly related to flumazenil and cause of death to be due to ingestion of a lethal dose of TCAs [20].

Seizure is a well-known and potential lethal AE to flumazenil. Seizures are not considered to be the result of a direct toxic effect of flumazenil but due to reversal of the anticonvulsant effect of the benzodiazepine in the presence of pro-convulsive drugs or other predispositions to seizures.

In our meta-analyses, three cases of seizures were reported [20,28]. Two of these patients had multi-drug intoxication, both with positive test for pro-convulsive drugs including TCAs and propoxyphene [20,28]. There is no information on possible co-ingested drugs for the third patient [20]. Additionally, four patients developed seizures during the open phase of the trial [20,24,28]. Review of available case reports documented another 13 cases of seizures related to flumazenil treatment [14,16,34,36,39–46]. Eleven of these cases had a multi-drug intoxication, which in eight cases involved TCAs.

Known or suspected intoxication with TCAs or other pro-convulsive drugs is a contra-indication for the use of flumazenil [47]. In a retrospective study involving 43 patients with flumazenil-induced seizures, 18 patients (42%) had an ingested overdose of TCAs and, of these, three patients died [48]. This study also concludes that patients with a higher risk of developing seizures after the administration of flumazenil include patients who have ingested TCAs, patients who have been treated with benzodiazepines for a seizure disorder or an acute convulsive episode, patients with concurrent major sedative-hypnotic drug withdrawal, patients who have recently been treated with repeated doses of parenteral benzodiazepines and intoxicated patients with myoclonic jerking or seizure activity before flumazenil administration [48]. The study found no relationship between the dose of flumazenil and the development of seizures [48].

With the available data, it is not possible to conclude on any relationship between flumazenil dose and development of AEs. Likewise, most included studies did not allow extraction of data on the time relation between the administration of flumazenil and the occurrence of AEs. However, a review of available case reports indicates that AEs occur within short time of the last flumazenil dose and all (S)AEs are reported

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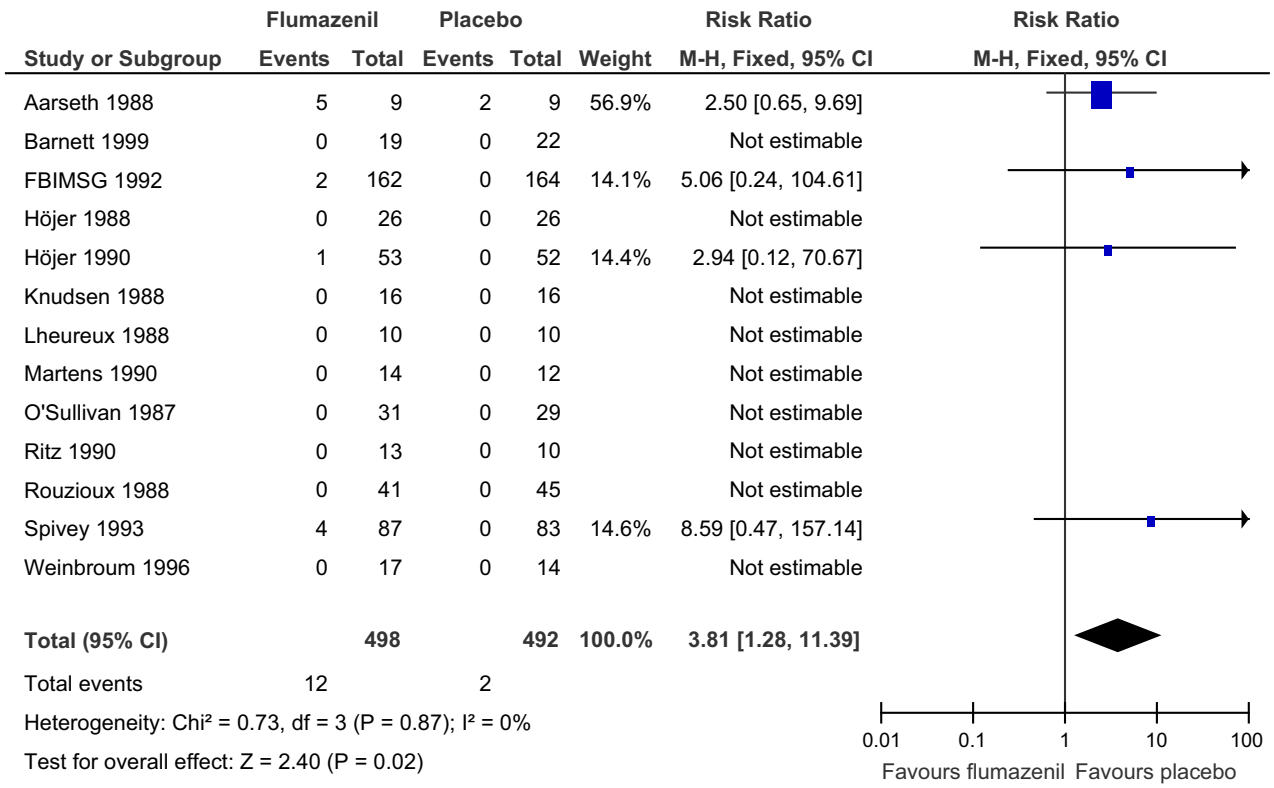
Flumazenil
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Aarseth 1988 5 9 2 9 56.9% 2.50 [0.65, 9.69]
Barnett 1999 0 19 0 22 Not estimable
FBIMSG 1992 2 162 0 164 14.1% 5.06 [0.24, 104.61]
Höjer 1988 0 26 0 26 Not estimable
Höjer 1990 1 53 0 52 14.4% 2.94 [0.12, 70.67]
Knudsen 1988 0 16 0 16 Not estimable
Lheureux 1988 0 10 0 10 Not estimable
Martens 1990 0 14 0 12 Not estimable
O'Sullivan 1987 0 31 0 29 Not estimable
Ritz 1990 0 13 0 10 Not estimable
Rouzioux 1988 0 41 0 45 Not estimable
Spivey 1993 4 87 0 83 14.6% 8.59 [0.47, 157.14]
Weinbroum 1996 0 17 0 14 Not estimable
Total (95% CI) 498 492 100.0% 3.81 [1.28, 11.39]
Total events 12 2
Heterogeneity: Chi² = 0.73, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 2.40 (P = 0.02)
0.01 0.1 1 10 100
Favours flumazenil Favours placebo

Fig. 2. Forrest plot, serious adverse events.

within 10 min. from the termination of flumazenil injection [14–16,34–37,39–41,43–46,49,50].

Flumazenil can be used both as a therapeutic and as a diagnostic tool in suspected benzodiazepine intoxication. The effect of flumazenil is well-established [4,19,21–24,26]. Flumazenil was statistically significantly more effective in the reversal of coma (SMD 1.12; 95% CI: 0.69–1.56) [13]. However, it is unclear whether an increase in GCS results in less morbidity and better outcome. Improvement in coma scale might be a surrogate parameter. Intoxication with benzodiazepines is very seldom life-threatening, although the drug has a respiratory depressant effect, and intoxication might result in the need of mechanical ventilation.

The diagnostic purpose with the use of flumazenil is controversial. Several studies have shown that flumazenil is a useful diagnostic tool when applied in unconscious patients [19,23,27]. It is also speculated that the use of flumazenil might reduce other resource-demanding and potentially harmful diagnostic interventions [22,29], mechanical ventilation and endotracheal intubation [20,27] and need of intensive care observation [22,26]. Moreover, a conscious patient might be able to provide important information about co-ingested drugs and thereby optimize treatment.

Two of the studies included in the present meta-analyses investigated the diagnostic efficacy, usefulness and safety of flumazenil [11,29]. One study included 31 patients in the double-blind phase (17 treated with flumazenil and 14 treated with placebo). This study demonstrated that flumazenil treatment resulted in safe extubation of five patients and endotracheal intubations could be avoided in another three patients [29]. The other study did not provide information on avoided intubations although blood gas tensions improved significantly after flumazenil treatment ($p < 0.01$) [11]. This study also found that significantly more patients treated with flumazenil compared with placebo were able to give valuable information on drug ingestion (40% *versus* 0.2%; $p < 0.001$) [11]. The question remains whether this justifies diagnostic treatment with a drug with potentially harmful (S)AEs.

It is of utmost importance carefully to consider for every individual patient the potential harms and benefits for the use of flumazenil. The use of flumazenil should be more restrictive in patients at risk of convulsions and cardiac arrhythmias and not threatened by respiratory depression.

Conclusion

Our results indicate that the use of flumazenil in a population admitted at the emergency department with suspected or known benzodiazepine intoxication is associated with a significantly increased risk of (serious) adverse events compared with placebo.

With the present knowledge, we advise that flumazenil should not be used routinely when treating patients with known or suspected benzodiazepine intoxication. The harms and benefits should be considered carefully in every patient, and all patients should be observed for (serious) adverse events.

A large, randomised, placebo-controlled trial with a sufficient observation time to observe later occurring adverse

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effects (e.g. aspiration pneumonia) is desired as this might allow more firm conclusions.

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